

STIC-ILL

RC261.A1 I57

Adom

From: Davis, Minh-Tam
Sent: Thursday, July 17, 2003 4:47 PM
To: STIC-ILL
Subj ct: reprint request for 09/857691

1) Wu HC, 1994, Intl J Cancer (US), 57(3): 406-12.

2) Shona Lang, 1998, European urology, 34(3): 286

3) Berthon, P, 1995, Intl J Oncology, 6(2): 333-343.

4) Santra S; Sood A K; Ghosh S K

Department of Life Sciences, Indiana State University, Terre Haute, IN
47809, USA.

Cancer immunology, immunotherapy - CII (GERMANY) Nov 1999, 48 (8)
p421-9, ISSN 0340-7004 Journal Code: 8605732

Thank you.

MINH TAM DAVIS

ART UNIT 1642, ROOM 8A01, MB 8E12

305-2008

Author(s): BERTHON P; CUSSENOT O; HOPWOOD L; LEDUC A; MAITLAND NJ
Corporate Source: UNIV YORK, DEPT BIOL, CANC RES UNIT/YORK YO1 5DD/N
YORKSHIRE/ENGLAND/; HOP ST LOUIS, DEPT UROL/F-75475 PARIS 10//FRANCE/
Journal: INTERNATIONAL JOURNAL OF ONCOLOGY, 1995, V6, N2 (FEB), P
333-343

ISSN: 1019-6439

Language: ENGLISH Document Type: ARTICLE

Abstract: To study mesenchymal-epithelial interactions associated with the normal and pathological human prostate, we have developed a model of well differentiated human prostate epithelial and fibroblastic cells. Normal human prostatic cells, either of epithelial or fibroblastic origins were successfully transfected with SV40 and strains with extended lifespan were selected until the crisis was reached, within 20 and 30 passages for the epithelial and fibroblastic cells, respectively. Only a few clones emerged from the crisis: PNT1A (Cussenot et al: J Urol 143: 881-886, 1991), PNT1B and PNT2 epithelial cell lines. Successful immortalisation was achieved only with SV40 expressing both large T and small t oncogenes, while attempts to immortalise with a vector expressing SV40 large T alone have given a few strains showing no extended lifespan and no cells which overcame the crisis. A PNT2 subclone named PNT2-LSD which developed spontaneously (less serum dependent) was selected, characterised and included in the analysed series. The epithelial cell lines displayed a differentiation pattern which has been classified as follows (from high to low): PNT2>PNT2-LSD>PNT1A>PNT1B. Differentiation features studied were (i) the colony-forming ability of the PNT2 and PNT2-LSD compared to PNT1A and PNT1B, (ii) their respective doubling time of 39, 29, 30 and 28 hours, (iii) their decreasing serum dependency, (iv) the expression of cytokeratin 19 (a feature of well differentiated luminal cells of the glandular prostate) for PNT2 and PNT2-LSD. Furthermore, the mesenchymal derived pflsv1 cells were confirmed to be of fibroblastic nature. None of the cell lines analysed showed any tumourigenicity in nude mice over a period of 12 months. Serum deprivation and direct steroid withdrawal during the culture triggered cell death by apoptosis, an event which could be overcome by EGF stimulation, particularly for the well differentiated PNT2 cells. This interesting characteristic, which is similar to the high apoptotic rate observed *in vivo* for normal prostate, particularly after castration should lead, together with the other properties of these cell lines, to a better understanding of the biology of the different cell compartments involved in the progression of prostate towards neoplasia.

, 1995

...Abstract: from the crisis: PNT1A (Cussenot et al: J Urol 143: 881-886, 1991), PNT1B and PNT2 epithelial cell lines. Successful immortalisation was achieved only with SV40 expressing both large T and ...

...a few strains showing no extended lifespan and no cells which overcame the crisis. A PNT2 subclone named PNT2-LSD which developed spontaneously (less serum dependent) was selected, characterised and included in the analysed...

...lines displayed a differentiation pattern which has been classified as follows (from high to low): PNT2>PNT2-LSD>PNT1A>PNT1B. Differentiation features studied were (i) the colony-forming ability of the PNT2 and PNT2-LSD compared to PNT1A and PNT1B, (ii) their respective doubling time of 39, 29, 30...

...of cytokeratin 19 (a feature of well differentiated luminal cells of the glandular prostate) for PNT2 and PNT2-LSD. Furthermore, the mesenchymal derived pflsv1 cells were confirmed to be of fibroblastic nature. None...

...apoptosis, an event which could be overcome by EGF stimulation,
particularly for the well differentiated PNT2 cells. This
interesting characteristic, which is similar to the high apoptotic rate
observed *in vivo*...

?

908464 22656977 PMID: 12772188

Expression of androgen receptor coactivators in normal and cancer **prostate** tissues and cultured **cell lines**.

Mestayer C; Blanchere M; Jaubert F; Dufour B; Mowszowicz I

Laboratoire de Recherche sur la Physiologie et la Pathologie Gonadique, Service d'Endocrinologie et Medecine de la Reproduction, Faculte de medecine Necker-Enfants Malades, Paris, France.

Prostate (United States) Aug 1 2003, 56 (3) p192-200, ISSN 0270-4137 Journal Code: 8101368

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: In Process

BACKGROUND: In **prostate** cancer **cell lines**, androgen receptor (AR) coactivators modulate the transcriptional activity of AR. However, very little is known about their expression in normal **prostate** tissue and during progression to cancer. **METHODS:** AR and coactivators ARA54, ARA55, ARA70, and SRC1 RNA were analyzed by RT-PCR in normal and tumoral tissues of the same **prostate**, in **prostate cell lines**, and after hormonal **treatments** of **prostate** epithelial cells. **RESULTS:** AR-coactivators were expressed in normal and tumoral tissues and in cultured **prostate** cells; only ARA55 expression was decreased in tumoral relative to normal tissue of all seven **prostates** analyzed. It was not expressed in LNCaP and DU145 cancer cells and low in **PNT2** immortalized cells in which all coactivator's expression were down regulated by DHT and up regulated by E2. In addition, coactivator's expression was increased in hyperplastic relative to normal **prostate** fibroblasts. **CONCLUSIONS:** ARA55 is both an AR coactivator and a focal adhesion protein (Hic-5). Its role in the progression of **prostate** carcinoma may therefore involve these two different functions. Its decrease in cancer tissue suggests that it plays a different role than that expected, namely, facilitate cell proliferation and therefore mobility and metastasis. **Prostate** 56: 192-200, 2003. Copyright 2003 Wiley-Liss, Inc.

Expression of androgen receptor coactivators in normal and cancer **prostate** tissues and cultured **cell lines**.

? s cell(5n)line??

Processing

4768304 CELL

2614078 LINE??

S1 797182 CELL(5N)LINE??

? s prostate

S2 150910 PROSTATE

? s s1 and s2

797182 S1

150910 S2

S3 17315 S1 AND S2

? s treat? or therap?

Processing

Processing

4491410 TREAT?

3695589 THERAP?

S4 6638182 TREAT? OR THERAP?

? s s3 and s4

17315 S3

6638182 S4

S5 7218 S3 AND S4

? s pnt2 or 95012613

62 PNT2

0 95012613

S6 62 PNT2 OR 95012613

? s s5 and s6

7218 S5

62 S6

S7 12 S5 AND S6

? rd

>>>Duplicate detection is not supported for File 340.

Dialog Acc No: 1038779 IFI Acc No: 7621447

Document Type: C

PHARMACEUTICAL PREPARATIONS; PALLIATIVE **TREATMENT** OF ENDOMETRIAL CARCINOMA, PROGESTERONES

Inventors: PETROW VLADIMIR (N/A)

Assignee: BRITISH DRUG HOUSES LTD GB

Assignee Code: 11496

Publication (No,Date), Applic (No,Date):

US 3988447 19761026 US 63316466 19631015

Publication Kind: A

Calculated Expiration: 19931026

Priority Applic(No,Date): US 63316466 19631015

Abstract: The invention relates to pharmaceutical preparation containing a 17a-acyloxy-6-methyl-16-methylene-pregna-4,6-diene-3,20-dione compound as an active ingredient, and to the use of such preparations for the palliative **treatment** and control of certain types of neoplasmin conditions.

...PALLIATIVE **TREATMENT** OF ENDOMETRIAL CARCINOMA, PROGESTERONES

Publication (No,Date), Applic (No,Date):

...19761026

Abstract: ...compound as an active ingredient, and to the use of such preparations for the palliative **treatment** and control of certain types of neoplasmin conditions.

Exemplary Claim: 5. A METHOD FOR THE PALLIATIVE **TREATMENT** OF ENDOMETRIAL CARCINOMA COMPRISING ORALLY ADMINISTERING TO A HUMAN FEMALE AFFLICTED WITH SAID ENDOMETRIAL CARCINOMA...

Non-exemplary Claims: 1. A method for palliative **treatment** of endometrial carcinoma comprising: administering to the human female afflicted with said endometrial carcinoma a...

...6. A method for palliative **treatment** of acute monocytic leukemia in animals comprising: administering to the animal afflicted with said leukemia...

...7. A method for palliative **treatment** of prostate squamous cell carcinoma in animals comprising: administering to the animal afflicted with said prostate squamous cell carcinoma a daily dosage of from about 1 to 40 mg./kg. of...

...8. A method for palliative **treatment** of mammary adenocarcinoma in animals comprising: administering to the animal afflicted with said mammary adenocarcinoma...

? log off

17jul03 11:57:15 User231882 Session D1196.3

\$8.36 2.612 DialUnits File155

\$2.73 13 Type(s) in Format 4 (UDF)

\$2.73 13 Types

\$11.09 Estimated cost File155

\$9.88 1.765 DialUnits File55

\$3.50 2 Type(s) in Format 3 (UDF)

\$3.50 2 Types

\$13.38 Estimated cost File55

\$35.83 1.937 DialUnits File34

\$10.70 2 Type(s) in Format 4 (UDF)

\$37.45 7 Type(s) in Format 55 (UDF)

\$48.15 9 Types

\$83.98 Estimated cost File34

\$10.82 0.585 DialUnits File434

\$5.35 1 Type(s) in Format 3 (UDF)
 \$5.35 1 Types
\$16.17 Estimated cost File434
 \$27.87 1.769 DialUnits File340
 \$72.15 37 Type(s) in Format 4 (UDF)
 \$72.15 37 Types
\$100.02 Estimated cost File340
 OneSearch, 5 files, 8.667 DialUnits FileOS
 \$3.02 TELNET
\$227.66 Estimated cost this search
\$227.73 Estimated total session cost 8.899 DialUnits
Logoff: level 02.17.00 D 11:57:15

156743 94222618 PMID: 8169003

Derivation of androgen-independent human LNCaP prostatic cancer cell sublines: role of bone stromal cells.

Wu H C; Hsieh J T; Gleave M E; Brown N M; Pathak S; Chung L W

Department of Urology, University of Texas M.D. Anderson Cancer Center, Houston 77030.

International journal of cancer. Journal international du cancer (UNITED STATES) May 1 1994, 57 (3) p406-12, ISSN 0020-7136

Journal Code: 0042124

Contract/Grant No.: CA56307; CA; NCI; DK38649; DK; NIDDK

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

7/17

A model of human **prostate** cancer was established to study cellular interaction between **prostate** cancer and bone stroma in vivo. In this model, subcutaneous co-injection of 2 non-tumorigenic human cell lines--LNCaP, a **prostate** cancer cell line, and MS, a bone stromal cell-line--into intact adult male mice resulted in formation of carcinomas that secreted **prostate**-specific antigen (PSA), a clinically useful human serum **prostate** cancer marker. In castrated hosts, upon cellular interaction with bone fibroblasts, we observed the progression of these tumors from an androgen-dependent (AD) to an androgen-independent state (AI). We derived 4 LNCaP cell sublines from the chimeric LNCaP/MS tumors: the M subline from intact hosts and the C4, C4-2 and C5 sublines from castrated hosts. The LNCaP sublines had chromosomal markers similar to those of the parental LNCaP cells and distinctly different from those of the MS bone stromal cell line. Although the parental and derived cell lines expressed similar steady-state levels of ornithine decarboxylase transcript, the sublines expressed 5- to 10-fold higher basal steady-state levels of PSA transcript than did the parental LNCaP cell line. The LNCaP sublines formed 13- to 26-fold more soft-agar colonies than the parental LNCaP cell line. The sublines became tumorigenic, yielding an incidence of tumors in intact athymic mice of 7-75%. The LNCaP sublines C4 and C5 (but not the parental and M cell line) formed tumors in castrated hosts when co-injected with bone fibroblasts. A second-generation LNCaP subline, C4-2, was derived from a chimeric tumor induced by co-inoculating castrated mouse with C4 cells and MS cells. We found that C4-2 subline was tumorigenic when inoculated into castrated hosts in the absence of inductive fibroblasts. Moreover, C4-2 was the only subline capable of forming soft-agar colonies when cultured in serum-free medium. In comparison with the parental LNCaP cells, the C4-2 subline expressed lower steady-state levels of androgen receptor (AR) protein and mRNA transcript and lost its androgen responsiveness in vitro. Our results suggest that certain genetic traits of **prostate** cancer cells may be selected or altered through an "adaptive" mechanism that involves cellular interaction with the bone stromal cells.

May 1 1994,

A model of human **prostate** cancer was established to study cellular interaction between **prostate** cancer and bone stroma in vivo. In this model, subcutaneous co-injection of 2 non-tumorigenic human cell lines--LNCaP, a **prostate** cancer cell line, and MS, a bone stromal cell-line--into intact adult male mice resulted in formation of carcinomas that secreted **prostate**-specific antigen (PSA), a clinically useful human serum **prostate** cancer marker. In castrated hosts, upon cellular interaction with bone fibroblasts, we observed the progression...

... and lost its androgen responsiveness in vitro. Our results suggest that certain genetic traits of **prostate** cancer cells may be selected or altered through an "adaptive" mechanism that involves cellular interaction ...

5/3,K,AB/14 (Item 14 from file: 155)
DIALOG(R) File 155:MEDLINE(R)
(c) format only 2003 The Dialog Corp. All rts. reserv.

08072075 94137823 PMID: 8305530

Purification and characterization of IL6-PE4E, a recombinant fusion of interleukin 6 with Pseudomonas exotoxin.

Kreitman R J; Pastan I

Laboratory of Molecular Biology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892.

Bioconjugate chemistry (UNITED STATES) Nov-Dec 1993, 4 (6)
p581-5, ISSN 1043-1802 Journal Code: 9010319

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

We have developed a procedure to purify the recombinant fusion toxin IL6-PE4E from Escherichia coli which results in a high yield of fully active monomeric protein of high purity and very low endotoxin content. The chimeric toxin is composed of human interleukin 6 (IL6) fused to a

740018 20019955 PMID: 10550546

Cytotoxic effector T cells elicited by the killed tumor **vaccine** differ significantly from the effectors generated during active growth of a murine B-cell lymphoma.

Santra S; Sood A K; Ghosh S K

Department of Life Sciences, Indiana State University, Terre Haute, IN 47809, USA.

Cancer immunology, immunotherapy - CII (GERMANY) Nov 1999, 48 (8) 7/17
p421-9, ISSN 0340-7004 Journal Code: 8605732

Contract/Grant No.: R15 CA70914; CA; NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Active specific immunotherapy of neoplastic diseases is an elusive goal. Using a murine B lymphoma 2C3, we showed that vaccination with the **killed tumor cells** effectively induces protective immunity and a cytotoxic T cell (CTL) response. Similar protection, however, is rarely observed in mice bearing live tumor cells. These animals usually succumb to the progressively growing tumor. In this study, we inquired whether the splenic CTL induced during tumor progression in mice differ from those evoked by the **killed tumor cells**. Here we demonstrate that the CTL generated following vaccination are significantly different from those induced in the tumor-bearing hosts. Adding to the complexity, the CTL from the early tumor bearers also differ significantly from those induced at the late stages. These differences are based on their cytotoxic activity, MHC allele specificity, mitogen responsiveness, cytokine secretion profile and T cell receptor Vbeta gene expression. The results clearly indicate that passive immunization with killed tumor is most effective, possibly because the CTL induced are not subject to the same regulatory pressure as those induced during active tumor growth. This decreasing effectiveness of CTL could be due to greater variability in antigenic stimulus, less involvement of innate immunity, changes in cytokine milieu and/or costimulatory factors.

Cytotoxic effector T cells eli

20/3,K,AB/13 (Item 5 from file: 340)
DIALOG(R)File 340:CLAIMS(R)/US Patent
(c) 2003 IFI/CLAIMS(R). All rts. reserv.

Dialog Acc No: 2087080 IFI Acc No: 9022843
Document Type: C
USE OF TUMOR NECROSIS FACTOR (TNF) AS AN ADJUVANT; IMMUNOLOGICAL RESPONSE
Inventors: Shepard H Michael (US); Talmadge James E (US)
Assignee: Genentech Inc
Assignee Code: 07579
Publication (No,Date), Applic (No,Date):
US 4963354 19901016 US 877075 19870121
Publication Kind: A
Calculated Expiration: 20071016
(Cited in 024 later patents)
Priority Applic(No,Date): US 877075 19870121

Abstract: Tumor necrosis factors, alone or together with cytokines such as IL-1 or INF- gamma , are capable of serving as non-toxic **vaccine** adjuvants.

Abstract: ...cytokines such as IL-1 or INF- gamma , are capable of serving as non-toxic **vaccine** adjuvants.

Non-exemplary Claims: ...6. The method of claim 2 wherein the substance is a **killed tumor cell**.

?

Dialog Acc No: 3343476 IFI Acc No: 0019637

Document Type: C

IMMUNOSTIMULATING AND **VACCINE** COMPOSITIONS EMPLOYING SAPONIN ANALOG
ADJUVANTS AND USES THEREOF; COMPRISING ONE OR MORE BACTERIAL, VIRAL OR
TUMOR-ASSOCIATED ANTIGENS; AND ONE OR MORE SAPONIN-LIOPHILE CONJUGATE

Inventors: Marciani Dante J (US)

Assignee: Galenica Pharmaceuticals Inc

Assignee Code: 51350

Publication (No,Date), Applic (No,Date):

US 6080725 20000627 US 99290606 19990413

Publication Kind: A

Calculated Expiration: 20180520

Cont.-in-part Pub(No),Applic(No,Date): US 5977081

US 9881647

19980520

Priority Applic(No,Date): US 99290606 19990413; US 9881647 19980520

Provisional Applic(No,Date): US 60-47129 19970520

Abstract: The present invention is directed to vaccines comprising (1) one or more bacterial, viral or tumor-associated antigens; and (2) one or more saponin-lipophile conjugate in which a lipophilic moiety such as a lipid, fatty acid, polyethylene glycol or terpene is covalently attached to a non-acylated or desacylated triterpene saponin via a carboxyl group present on the 3-O-glucuronic acid of the triterpene saponin. The attachment of a lipophile moiety to the 3-O-glucuronic acid of a saponin such as Quillaja desacylsaponin, lucyoside P, or saponin from Gypsophila, Saponaria and Acanthophyllum enhances their adjuvant effects on humoral and cell mediated immunity. Additionally, the attachment of a lipophile moiety to the 3-O-glucuronic acid residue of nonor des-acylsaponin yields a saponin analog that is easier to purify, less toxic, chemically more stable, and possesses equal or better adjuvant properties than the original saponin.

IMMUNOSTIMULATING AND **VACCINE** COMPOSITIONS EMPLOYING SAPONIN ANALOG
ADJUVANTS AND USES THEREOF...

Exemplary Claim: D R A W I N G

1. A **vaccine** for human or veterinary use, comprising: (a) one or more bacterial, viral, protozoal or tumor...

Non-exemplary Claims: 2. The **vaccine** of claim 1, wherein said saponin-lipophile conjugate is a conjugate of (1) Quillaja desacylsaponin...

...3. The **vaccine** of claim 2, wherein said lipophilic moiety of said saponin-lipophile conjugate is a residue...

...4. The **vaccine** of claim 3, wherein said lipophilic moiety of said saponin-lipophile conjugate is a residue...

...5. The **vaccine** of claim 4, wherein said lipophilic moiety is a residue of nonylamine or dodecylamine...

...6. The **vaccine** of claim 3, wherein said lipophilic moiety of said saponin-lipophile conjugate is a residue...

...7. The **vaccine** of claim 6, wherein said fatty acid is selected from the group consisting of lauric...

...8. The **vaccine** of claim 3, wherein said lipophile moiety of said saponin-lipophile conjugate is a residue...

...9. The **vaccine** of claim 3, wherein said lipophilic moiety of said saponin-lipophile conjugate is a phosphoglyceride...

...11. The **vaccine** of claim 1, wherein said one or more antigens are

bacterial antigens...

- ...12. The **vaccine** of claim 11, wherein said bacterial antigens are antigens associated with a bacterium selected from 13. The **vaccine** of claim 1, wherein said one or more antigens are viral-associated antigens...
- ...14. The **vaccine** of claim 13, wherein said viral-associated antigens are antigens associated with a virus selected...
- ...15. The **vaccine** of claim 1, wherein said one or more antigens are tumor-associated antigens...
- ...16. The **vaccine** of claim 15, wherein said tumor-associated antigens are antigens selected from the group consisting of **killed tumor cells** and lysates thereof, MAGE-1, MAGE-3 and peptide fragments thereof; Human chorionic gonadotropin and...
- ...17. The **vaccine** of claim 1, wherein said one or more antigens are native, recombinant or synthetic...
- ...18. The **vaccine** of claim 1, wherein said one or more antigens are employed, either free, non-covalently...
- ...19. The **vaccine** of claim 1, wherein said saponin-lipophile conjugate is represented by Formula II...
- ...20. The **vaccine** of claim 19, wherein X is ...21. The **vaccine** of claim 19, wherein X is a linking group selected from the group consisting of...
- ...22. The **vaccine** of claim 19, wherein R3 is selected from the group consisting of a C4 -C30...
- ...23. The **vaccine** of claim 22, wherein X is NH or NR4, where R4 is C1 -C3 alkyl...
- ...24. The **vaccine** of claim 23, wherein X is N

20/3,K,AB/9 (Item 1 from file: 340)
DIALOG(R) File 340:CLAIMS(R)/US Patent
(c) 2003 IFI/CLAIMS(R). All rts. reserv.

Dialog Acc No: 10364157 IFI Acc No: 2003-0108574 IFI Acc No: 2003-0030644
Document Type: C
CARBOHYDRATE-BASED WHOLE CELL CANCER VACCINES
Inventors: Jennings Harold J (CA); Liu Tianmin (CA); Yang Qingling (CA)
Assignee: Unassigned Or Assigned To Individual
Assignee Code: 68000
Publication (No,Date), Applic (No,Date):
US 20030108574 20030612 US 2002224326 20020821
Publication Kind: A1
Priority Applic(No,Date): US 2002224326 20020821
Provisional Applic(No,Date): US 60-313466 20010821

Abstract: When tumor cells are incubated with N-propionyl mannosamine, the N-acetyl groups of their surface a2-8 polysialic acid are converted to N-propionyl groups. The resultant bio-engineered cancer cells can be killed and used as a allogenic or autologous therapy or **vaccine**. The presence of N-propionylated polysialic acid-specific antibodies is detected in animals immunized with the **vaccine** prior to tumor implantation. Mice immunized with the heat-killed **cancer cells** experience better protection against challenge with live autologous RMA-S cells than mice immunized with heat-killed autologous RMA-S cells. Killed cells having modified sialic acid groups on their surface may be used as an anti-cancer therapy or **vaccine** either alone or in combination with an anti-cancer compound, such as cyclophosphamide.

reprinted with permission by the Publisher. This material is protected by copyright and cannot be further reproduced or stored electronically without publisher permission and payment of a royalty fee for each copy made. All rights reserved.

vide closely-apposed cells with intercellular channels as passageways of ions and small molecules. Gap junction proteins (connexins) are encoded by a multifamily of highly conserved genes which have been recognized to behave as tumor suppressive elements [2]. This reinforces the conception that disturbance of GJIC may be important in carcinogenesis. However, the potential role of GJIC in development and growth of human cancerous prostate remains ill-defined. We have investigated GJIC in several human prostate epithelial cells, including primary cultures of nonneoplastic adult prostate epithelium, immortalized with HPV18 (RWPE-1), HPV18/KiRas (RWPE-2) or Ad12/SV40 (PWR-1E), as like as neoplastic LNCaP and DU145 cells. Normal rat liver F344 (WB1) cells were used as positive controls. Functional GJIC was inspected using either the Scrapie-Loading (SL) or the Fluorescence Recovery After Photobleaching (FRAP) analyses, based on a Ultima laser cytometer. The GJIC activity was expressed as the extent of diffusion of the Lucifer Yellow dye, or as the recovery of fluorescence over time (3–12 min) in photobleached cells from the surrounding unbleached cells, respectively. The data obtained indicate that neither immortalized RWPE-2 and PWR-1E cells, nor tumor LNCaP cells have functional GJIC, while, as expected, WB1 cells show a unimpaired GJIC activity. Equivalent results were obtained using either SL or FRAP approaches. However, FRAP analysis revealed a 10% recovery fluorescence in RWPE-1 cells after longer observation intervals (1 h). More important, preliminary data suggest that GJIC activity may be regulated in these systems by both forskolin and estrone, agents which have been shown to elevate intracellular cAMP levels. In addition, treatment of cells with 5 μ M lovastatin, which prevents p21 ras farnesylation [3], strongly induced GJIC activity and caused dramatic morphological changes in RWPE-1 and RWPE-2 cells, suggesting that this drug may be implicated in the regulation of both intercellular communication and differentiation of these systems. This evidence would imply that restoration of GJIC may represent a target for development of new strategies for prevention and/or treatment of human prostate cancer.

Studies partially supported by Italian AIRC and FIRC.

References

- 1 Beyer E. *Int Rev Cytol* 1993;137C:1–37.
- 2 Trosko J, Goodman J. *Mol Carcinog* 1994;11:8–12.
- 3 Casey PJ, Soliski PA, Der CJ, Buss JE. *Proc Natl Acad Sci USA* 1989;86:8323–8327.

110

IN VITRO MODELLING OF EPITHELIAL AND STROMAL INTERACTIONS IN NORMAL AND MALIGNANT PROSTATES

Lang Shona and N.J. Maitland

YCR Cancer Research Unit, Dept. Biology, University of York, Heslington, York, UK

At clinical presentation, prostate cancer is a very heterogeneous disease. This fact has held back the development of a diagnostic test to predict which tumours will progress to a life threatening stage. Previous evidence suggests that both stromal and epithelial elements of the prostate can contribute to the emergence of a malignant phenotype. Our aim is to study changes in epithelial: stromal interactions between normal and malignant primary cells, *in vitro*. We have estab-

lished this model using primary human fibroblasts from tumour (mFB) and non-tumour prostate tissues (bFB) and established cell lines representing epithelial cells of normal (PNT1 and PNT2) and tumour origins (PC-3, DU145, LNCaP). The effects of fibroblasts on epithelial growth were studied using direct and indirect (using cell culture inserts) co-cultures. Also, the growth of epithelia in media conditioned by fibroblasts was measured using the MTT assay. We studied epithelial cell morphology grown in collagen gels in the presence of media conditioned by fibroblasts (FCBM). The effect of fibroblasts on the invasive ability of epithelial cells was measured using matrigel invasion chambers and finally, the effect of media conditioned by fibroblasts on epithelial cell motility was measured using time lapse microscopy. The initial results indicate that epithelial cell line growth (whether in direct or indirect co-culture) is unaffected or inhibited by mFB ($n = 4$) and bFB ($n = 5$). No differences were observed between the response of normal or malignant epithelia or the use of bFB or mFB. In contrast, cell lines growing as spherical colonies in collagen gels were induced to branch (PNT1, PNT2 and DU145), scatter (PC-3) or were unaffected (LNCaP) in response to FCBM (bFB, $n = 2$). PNT2 were found to be the least and PC-3 the most invasive and motile of the cell lines. Fibroblast cultures (bFB, $n = 2$; mFB, $n = 2$) greatly enhance the motility and invasion of PC-3 but had only modest effects on PNT2. The results indicate that cell motility and invasion show the greatest disparity between normal and tumour epithelia, with cell lines.

111

FIBRONECTIN IS SECRETED BY LNCaP AND BY PRIMARY PROSTATIC STROMAL CELLS AND PLAYS A ROLE IN CELL ADHESION

M. Albrecht, Möschler, H. Renneberg, G. Wennemuth
G. Aumüller, L. Konrad

Institute of Anatomy and Cell Biology, Marburg, Germany

We examined the mRNA expression and synthesis of FN in cultures of LNCaP cells and in primary stromal prostate cells. RT-PCR analysis revealed FN transcripts in both cell types. Levels of FN were determined quantitatively by competitive ELISA. Primary stromal prostate cells released into the medium 1850 ng FN/ μ g DNA on day 1 with increasing levels during one week (4140 ng FN/ μ g DNA on day 6). In contrast, LNCaP cells released 600 ng FN/ μ g DNA on day 1 and 1660 ng FN/ μ g DNA on day 6. These data were further substantiated by the immunohistochemical localization of FN in the stromal and epithelial cells *in vivo*. Perturbation experiments demonstrated the crucial role of FN in cell adhesion. Blocking FN with anti-FN antibodies resulted in a significant decrease in adhesion for the LNCaP cells and a change in morphology for the primary stromal cells. From these data we conclude that FN is produced and secreted mainly by the stromal cells of the human prostate and is involved in epithelial cell adhesion.

11493714 98377861 PMID: 9714059

Establishing human prostate cancer cell xenografts in bone: induction of osteoblastic reaction by prostate-specific antigen-producing tumors in athymic and SCID/bg mice using LNCaP and lineage-derived metastatic sublines.

Wu T T; Sikes R A; Cui Q; Thalmann G N; Kao C; Murphy C F; Yang H; Zhau H E; Balian G; Chung L W

Department of Urology, University of Virginia Health Sciences Center, Charlottesville 22908, USA.

International journal of cancer. Journal international du cancer (UNITED STATES) Sep 11 1998, 77 (6) p887-94, ISSN 0020-7136 Journal Code: 0042124

Contract/Grant No.: CA-63341; CA; NCI; CA-64863; CA; NCI; DK-47596; DK; NIDDK

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

LNCaP lineage-derived human prostate cancer cell lines C4-2 and C4-2B4 acquire androgen independence and osseous metastatic potential in vivo. Using C4-2 and C4-2B4 the goals of the current investigation were 1) to establish an ideal bone xenograft model for prostate cancer cells in intact athymic or SCID/bg mice using an intraosseous route of tumor cell administration and 2) to compare prostate cancer metastasis by administering cells either through intravenous (i.v.) or intracardiac administration in athymic or SCID/bg mice. Subsequent to tumor cell administration, prostate cancer growth in the skeleton was assessed by radiographic bone density, serum prostate-specific antigen (PSA) levels, presence of hematogenous prostate cancer cells and histopathologic evaluation of tumor specimens in the lymph node and skeleton. Our results show that whereas LNCaP cells injected intracardially failed to develop metastasis, C4-2 cells injected similarly had the highest metastatic capability in SCID/bg mice. Retroperitoneal and mediastinal lymph node metastases were noted in 3/7 animals, whereas 2/7 animals developed osteoblastic spine metastases. Intracardiac injection of C4-2 in athymic hosts produced spinal metastases in 1/5 animals at 8-12 weeks post-injection; PC-3 injected intracardially also metastasized to the bone but yielded osteolytic responses. Intravenous injection of either LNCaP or C4-2 failed to establish tumor colonies. Intrailiac injection of C4-2 but not LNCaP nor C4-2B4 cells in athymic mice established rapidly growing tumors in 4/8 animals at 2-7 weeks after inoculation. Intrafemoral injection of C4-2 (9/16) and C4-2B4 (5/18) but not LNCaP (0/13) cells resulted in the development of osteoblastic bone lesions in athymic mice (mean: 6 weeks, range: 3-12 weeks). In SCID/bg mice, intrafemoral injection of LNCaP (6/8), C4-2 (8/8) and C4-2B4 (8/8) cells formed PSA-producing, osteoblastic tumors in the bone marrow space within 3-5 weeks after tumor cell inoculation. A stepwise increase of serum PSA was detected in all animals. Reverse transcription-polymerase chain reaction (RT-PCR) to detect hematogenously disseminated prostate cancer cells could not be correlated to either serum PSA level or histological evidence of tumor cells in the marrow space. We have thus established a PSA-producing and osteoblastic human prostate cancer xenograft model in mice.

... evaluation of tumor specimens in the lymph node and skeleton. Our results show that whereas LNCaP cells injected intracardially failed to develop metastasis, C4-2 cells injected similarly had the highest metastatic capability...

... injection; PC-3 injected intracardially also metastasized to the bone but yielded osteolytic responses. Intravenous injection of either LNCaP or C4-2 failed to establish tumor colonies. Intrailiac injection of C4-2 but not LNCaP nor C4-2B4 cells in athymic

7/18

mice established rapidly growing tumors in 4/8 animals...
... in athymic mice (mean: 6 weeks, range: 3-12 weeks). In SCID/bg mice,
intrafemoral **injection** of **LNCaP** (6/8), C4-2 (8/8) and C4-2B4
(8/8) cells formed PSA-producing...
?

11/3,K,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2003 The Dialog Corp. All rts. reserv.

09180976 20487198 PMID: 11034385

Dendritic cells capture killed tumor cells and present their antigens to elicit tumor-specific immune responses.

Nouri-Shirazi M; Banchereau J; Bell D; Burkeholder S; Kraus E T; Davoust J; Palucka K A

Baylor Institute for Immunology Research, Dallas, TX 75204, USA.

Journal of immunology (Baltimore, Md. - 1950) (UNITED STATES) Oct 1 2000, 165 (7) p3797-803, ISSN 0022-1767 Journal Code: 2985117R

Contract/Grant No.: CA78846-01A1; CA; NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Due to their capacity to induce primary immune responses, dendritic cells (DC) are attractive vectors for immunotherapy of cancer. Yet the targeting of tumor Ags to DC remains a challenge. Here we show that immature human monocyte-derived DC capture various killed tumor cells, including Jurkat T cell lymphoma, malignant melanoma, and prostate carcinoma. DC loaded with killed tumor cells induce MHC class I- and class II-restricted proliferation of autologous CD8+ and CD4+ T cells, demonstrating cross-presentation of tumor cell-derived Ags. Furthermore, tumor-loaded DC elicit expansion of CTL with cytotoxic activity against the tumor cells used for immunization. CTL elicited by DC loaded with the PC3 prostate carcinoma cell bodies kill another prostate carcinoma cell line, DU145, suggesting recognition of shared Ags. Finally, CTL elicited by DC loaded with killed LNCap prostate carcinoma cells, which express prostate specific Ag (PSA), are able to kill PSA peptide-pulsed T2 cells. This demonstrates that induced CTL activity is not only due to alloantigens, and that alloantigens do not prevent the activation of T cells specific for tumor-associated Ags. This approach opens the possibility of using allogeneic tumor cells as a source of tumor Ag for antitumor therapies.

... cell line, DU145, suggesting recognition of shared Ags. Finally, CTL elicited by DC loaded with killed LNCap prostate carcinoma cells, which express prostate specific Ag (PSA), are able to kill PSA peptide...

?

1602487 99035190 PMID: 9816342

Selection of highly metastatic variants of different human prostatic carcinomas using orthotopic implantation in nude mice.

Pettaway C A; Pathak S; Greene G; Ramirez E; Wilson M R; Killion J J; Fidler I J

Departments of Urology and Cell Biology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030, USA.

Clinical cancer research - an official journal of the American Association for Cancer Research (UNITED STATES) Sep 1996, 2 (9)

p1627-36, ISSN 1078-0432 Journal Code: 9502500

Contract/Grant No.: CA 16672; CA; NCI; R35-CA42107; CA; NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The purpose of this study was to determine whether the implantation of human prostate cancer cells into the prostates of nude mice and their subsequent growth there can be used to select variants with increasing metastatic potential. PC-3M and LNCaP cells were injected into the prostates of athymic mice. Tumors from the prostate or lymph nodes were harvested, and cells were reinjected into the prostate. This cycle was repeated three to five times to yield cell lines PC-3M-Pro4, PC-3M-LN4, LNCaP-Pro3-5, and LNCaP-LN3-4. Parental and variant cells were injected into the prostates of nude mice. PC-3M-LN4 cells produced enhanced regional lymph node and distant organ metastasis as compared to PC-3M-Pro4 or PC-3M cells. After i.v. or intracardiac inoculation, PC-3M-LN4 cells produced a higher incidence of lung metastasis and bone metastasis, respectively, than PC-3M or PC-3M-Pro4 cells. Subsequent to implantation into the prostate, LNCaP-LN3 cells produced a higher incidence of regional lymph node metastases than LNCaP-Pro5 or LNCaP cells. After intrasplenic implantation, LNCaP-LN3 cells also yielded experimental liver metastases. The metastatic LNCaP-LN3 cells exhibited clonal karyotypic abnormalities, were less sensitive to androgen (in vitro and in vivo), and produced high levels of prostate-specific antigen. Collectively, the data show that the orthotopic implantation of human prostate cancer cell lines in nude mice is a relevant model with which to study the biology of prostate cancer metastasis and to select variant cell lines with enhanced metastatic potential.

5/3,K,AB/1 (Item 1 from file: 155)

DIALOG(R) File 155:MEDLINE(R)

(c) format only 2003 The Dialog Corp. All rts. reserv.

11497659 98381932 PMID: 9717832

Systemic interleukin 2 therapy for human **prostate** tumors in a nude mouse model.

Triest J A; Grignon D J; Cher M L; Kocheril S V; Montecillo E J; Talati B ; Tekyi-Mensah S; Pontes J E; Hillman G G

Department of Urology, Barbara Ann Karmanos Cancer Institute at Wayne State University School of Medicine and Harper Hospital, Detroit, Michigan 48201, USA.

Clinical cancer research - an official journal of the American Association for Cancer Research (UNITED STATES) Aug 1998, 4 (8)

p2009-14, ISSN 1078-0432 Journal Code: 9502500

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Once the regional lymph nodes become involved in **prostate** carcinoma, 85% of patients develop distant metastases within 5 years, and metastatic disease is difficult to treat. We have investigated the effect of systemic interleukin 2 (IL-2) treatment on metastatic **prostate** carcinoma using a xenograft tumor model. Cells from a PC-3/IF **cell line**, produced by intrafemoral **injection** of human PC-3 **prostate** carcinoma cells, were injected in the **prostate** of Balb/c nude mice. **Prostate** tumors and para-aortic lymph nodes were resected, and tumor cells were recultured and passaged in the **prostate** in vivo to produce new **cell lines**. On day 6 following prostatic **injection** of these **cell lines**, mice were treated with i.p. injections of IL-2 at 25,000-50,000 units/ day for 5 consecutive days. The effect of IL-2 on tumor progression was assessed, and histological studies were performed on **prostate** tumor and lymph node sections. The tumor **cell lines** generated by serial **prostate injection** were tumorigenic and metastasized to regional para-aortic lymph nodes. Tumors of 0.4 cm were obtained by day 16 and grew to 1-1.5 cm by day 40 with metastasis to para-aortic lymph nodes.

7/23/03

✓

```

-----
? s (administer? or inject?) (5n) (cell(w)line??)
Processing
Processing
      533849 ADMINISTER?
      993602 INJECT?
      4768304 CELL
      2614078 LINE??
S1      1973 (ADMINISTER? OR INJECT?) (5N) (CELL(W)LINE??)

```

```

? s prostate
S2      150910 PROSTATE

```

```

? s s1 and s2
      1973 S1
      150910 S2
S3      67 S1 AND S2

```

```

? rd
>>>Duplicate detection is not supported for File 340.

```

```

>>>Records from unsupported files will be retained in the RD set.
...examined 50 records (50)
...completed examining records
S4      38 RD (unique items)

```

```

? s s4 and py<=1998
Processing
Processing
      38 S4
      33599898 PY<=1998
S5      25 S4 AND PY<=1998
? t s5/3,k,ab/1-25

```

```

5/3,K,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2003 The Dialog Corp. All rts. reserv.

```

```

11497659 98381932 PMID: 9717832

```

Systemic interleukin 2 therapy for human **prostate** tumors in a nude mouse model.

Triest J A; Grignon D J; Cher M L; Kocheril S V; Montecillo E J; Talati B ; Tekyi-Mensah S; Pontes J E; Hillman G G

Department of Urology, Barbara Ann Karmanos Cancer Institute at Wayne State University School of Medicine and Harper Hospital, Detroit, Michigan 48201, USA.

Clinical cancer research - an official journal of the American Association for Cancer Research (UNITED STATES) Aug 1998, 4 (8)

p2009-14, ISSN 1078-0432 Journal Code: 9502500

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Once the regional lymph nodes become involved in **prostate** carcinoma, 85% of patients develop distant metastases within 5 years, and metastatic disease is difficult to treat. We have investigated the effect of systemic interleukin 2 (IL-2) treatment on metastatic **prostate** carcinoma using a xenograft tumor model. Cells from a PC-3/IF **cell line**, produced by intrafemoral **injection** of human PC-3 **prostate** carcinoma cells, were injected in the **prostate** of Balb/c nude mice. **Prostate** tumors and para-aortic lymph nodes were resected, and tumor cells were recultured and passaged in the **prostate** in vivo to produce new **cell lines**. On day 6 following prostatic **injection** of these **cell lines**, mice were treated with i.p. injections of IL-2 at 25,000-50,000 units/ day for 5 consecutive days. The effect of IL-2 on tumor progression was assessed, and histological studies were performed on **prostate** tumor and lymph node sections. The tumor **cell lines** generated by serial

prostate injection were tumorigenic and metastasized to regional para-aortic lymph nodes. Tumors of 0.4 cm were obtained by day 16 and grew to 1-1.5 cm by day 40 with metastasis to para-aortic lymph nodes. Following two to three weekly courses of 5 days of 25,000-40,000 units/day of IL-2, the growth of **prostate** tumors was inhibited by 94%. Higher doses of 50,000 units/ day were toxic. Histologically, **prostate** sections showed vascular damage manifested by multifocal hemorrhages and an influx of lymphocytes and polymorphonuclear cells into disintegrating tumors and areas of necrosis containing numerous apoptotic cells. In contrast to control mice, para-aortic lymph nodes were not enlarged in responding mice. These findings suggest that systemic IL-2 therapy can induce an antitumor response in **prostate** tumors and control their growth and metastasis.

Systemic interleukin 2 therapy for human **prostate** tumors in a nude mouse model.

Aug 1998,

Once the regional lymph nodes become involved in **prostate** carcinoma, 85% of patients develop distant metastases within 5 years, and metastatic disease is difficult...

... treat. We have investigated the effect of systemic interleukin 2 (IL-2) treatment on metastatic **prostate** carcinoma using a xenograft tumor model. Cells from a PC-3/IF **cell line**, produced by intrafemoral **injection** of human PC-3 **prostate** carcinoma cells, were injected in the **prostate** of Balb/c nude mice. **Prostate** tumors and para-aortic lymph nodes were resected, and tumor cells were recultured and passaged in the **prostate** in vivo to produce new **cell lines**. On day 6 following prostatic **injection** of these **cell lines**, mice were treated with i.p. injections of IL-2 at 25,000-50,000...

... effect of IL-2 on tumor progression was assessed, and histological studies were performed on **prostate** tumor and lymph node sections. The tumor **cell lines** generated by serial **prostate injection** were tumorigenic and metastasized to regional para-aortic

? ds

Set	Items	Description
S1	62	PNT2 OR (ECACC(2N)95012613)
S2	6638182	TREAT? OR THERAP?
S3	16	S1 AND S2
S4	8	RD (unique items)
S5	0	NIH(W)1542
S6	6	CP3TX
S7	3	RD (unique items)
S8	7795	PROSTATE(5N) (CELL(W)LINE??)
S9	31	S1 AND S8
S10	0	S9 AND S6
S11	0	S1 AND S6
S12	2148094	CANCER OR TUMOR
S13	3	S9 AND PY<=1998
S14	3	RD (unique items)

? s lnCap

S15 7982 LNCAp

? s s1 and s15

62 S1

7982 S15

S16 30 S1 AND S15

? rd

>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.

...completed examining records

S17 17 RD (unique items)

? s s17 and py<=1998

Processing

17 S17

33599898 PY<=1998

S18 4 S17 AND PY<=1998

? t s18/3,k,ab/1-4

18/3,K,AB/1 (Item 1 from file: 55)

DIALOG(R)File 55:Biosis Previews(R)

(c) 2003 BIOSIS. All rts. reserv.

11749414 BIOSIS NO.: 199800530110

In vitro modelling of epithelial and stromal interactions in normal and malignant prostates.

AUTHOR: Shona Lang; Maitland N J

AUTHOR ADDRESS: YCR Cancer Res. Unit, Dep. Biol., Univ. York, Heslington, York**UK

JOURNAL: European Urology 34 (3):p286 Sept., 1998

CONFERENCE/MEETING: 13th Congress of the European Society for Urological Oncology and Endocrinology Innsbruck, Austria October 1-3, 1998

ISSN: 0302-2838

RECORD TYPE: Citation

LANGUAGE: English

1998

1998

DESCRIPTORS:

...ORGANISMS: LNCaP (Hominidae...

...PNT2 (Animalia)

18/3,K,AB/2 (Item 2 from file: 55)

7/17

Set Items Description

? s pnt2 or (ECACC(2n)95012613)

62 PNT2
288 ECACC
0 95012613
0 ECACC(2N)95012613

S1 62 PNT2 OR (ECACC(2N)95012613)

? s treat? or therap?

Processing

Processing

4491410 TREAT?
3695589 THERAP?
S2 6638182 TREAT? OR THERAP?

? s s1 and s2

62 S1
6638182 S2
S3 16 S1 AND S2

? rd

>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.

...completed examining records

S4 8 RD (unique items)

? t s4/3,k,ab/1-8

? ds

Set	Items	Description
S1	62	PNT2 OR (ECACC(2N)95012613)
S2	6638182	TREAT? OR THERAP?
S3	16	S1 AND S2
S4	8	RD (unique items)

? s nih(w)1542

30211 NIH

533 1542

S5 0 NIH(W)1542

? s cp3Tx

S6 6 CP3TX

? rd

>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.

...completed examining records

S7 3 RD (unique items)

? t s7/3,k,ab/1-3

7/3,K,AB/1 (Item 1 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

(c) format only 2003 The Dialog Corp. All rts. reserv.

11926606 99370253 PMID: 10440875

Isochromosome 8q formation is associated with 8p loss of heterozygosity in a prostate cancer cell line.

Virgin J B; Hurley P M; Nahhas F A; Bebchuk K G; Mohamed A N; Sakr W A; Bright R K; Cher M L

Barbara Ann Karmanos Cancer Institute, Wayne State University, Detroit, Michigan, USA. jvirgin@med.wayne.edu

Prostate (UNITED STATES) Sep 15 1999, 41 (1) p49-57, ISSN 0270-4137
Journal Code: 8101368

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

BACKGROUND: In advanced prostate cancer, loss of chromosomal regions on 8p is frequently associated with gain of 8q. We studied the gross chromosomal abnormalities associated with 8p loss of heterozygosity (LOH) in the prostate tumor cell line 1542 CP3Tx. The cell line was previously established from a primary prostatic adenocarcinoma by immortalization with a recombinant retrovirus carrying the E6 and E7 genes of human papilloma virus type 16. Allelotyping studies demonstrated LOH at multiple markers on 8p. METHODS: To investigate the relationship of 8p LOH to gross chromosomal rearrangements, and to screen for other genetic abnormalities in 1542 CP3Tx, we used comparative genomic hybridization (CGH), conventional karyotyping, fluorescence in situ hybridization (FISH), and allelotyping. RESULTS: CGH revealed loss of the entire 8p arm, associated with gain of the entire 8q arm. Other abnormalities included chromosome 4 loss and chromosome 11 gain. The karyotype showed an isochromosome (8q), monosomy 4, and trisomy 11. FISH and allelotyping confirmed and extended these results. CONCLUSIONS: These results demonstrate that i(8q) formation is a mechanism for associated 8p loss and 8q gain in prostate cancer. Furthermore, the small number of chromosomal abnormalities in this cell line indicates that immortalization of low-passage cultures with viral oncogenes provides a method for obtaining cell lines for studying genetic abnormalities in prostate cancer.

Copyright 1999 Wiley-Liss, Inc.

... abnormalities associated with 8p loss of heterozygosity (LOH) in the prostate tumor cell line 1542 CP3Tx. The cell line was previously established from a primary prostatic adenocarcinoma by immortalization with

a...

... 8p LOH to gross chromosomal rearrangements, and to screen for other genetic abnormalities in 1542 CP3Tx, we used comparative genomic hybridization (CGH), conventional karyotyping, fluorescence in situ hybridization (FISH), and allelotyping...

7/3,K,AB/2 (Item 1 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

14017314 BIOSIS NO.: 200300011343

Drug resistance in prostate cancer cell lines is influenced by androgen dependence and p53 status.

AUTHOR: Serafin Antonio M; Akudugu John M; Bohm Lothar(a)
AUTHOR ADDRESS: (a)Department of Radiation Oncology, Radiobiology
Laboratory, Faculty of Health Sciences, Tygerberg Hospital, Tygerberg,
7505, South Africa**South Africa E-Mail: elb@sun.ac.za

JOURNAL: Urological Research 30 (5):p289-294 October 2002 2002

MEDIUM: print

ISSN: 0300-5623

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Chemotherapeutic drug resistance remains a significant obstacle in the control of prostate cancer. The influence of p53 and androgen status on the drug response of new cell lines from normal, benign and primary tumour epithelium was investigated. The prostate cell lines 1542-NPTX, BPH-1, 1542-CP3TX, 1532-CP2TX, 1535-CP1TX and LNCaP were exposed to TD50 doses of etoposide, vinblastine and estramustine for a period of 24 h and re-incubated for a further 4 days before measuring the cell viability by crystal violet vital dye staining assay. The virus-transformed cell lines were found to be approximately ten times more sensitive to etoposide and vinblastine than the non virus-transformed LNCaP cell line. Estramustine proved to be the least toxic drug. The LNCaP cell line emerged as DHT-sensitive against nanomolar concentrations of 5alpha-dihydrotestosterone in charcoal-stripped growth medium. The virus-transformed cell lines were DHT-insensitive. Induction of p21 by 60Co gamma-irradiation was used to assess the functionality of the p53 gene. p21 induction in the LNCaP cell line reached a peak 7.5 h post-irradiation. No significant p21 induction occurred in the virus-transformed cell lines. We show that the androgen-independent tumour cell lines are more sensitive to etoposide and vinblastine than the androgen dependent cell line, LNCaP. Except for LNCaP cells, etoposide and vinblastine were found to be three- to ten-fold more effective than estramustine. In the benign hyperplasia cell line, BPH-1, only etoposide is highly effective. Etoposide and vinblastine were found to effectively inactivate the androgen-independent cell lines, in which p53 is dysfunctional.

2002

...ABSTRACT: and primary tumour epithelium was investigated. The prostate cell lines 1542-NPTX, BPH-1, 1542-CP3TX, 1532-CP2TX, 1535-CP1TX and LNCaP were exposed to TD50 doses of etoposide, vinblastine and...

7/3,K,AB/3 (Item 2 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

13264381 BIOSIS NO.: 200100471530

Over expression of semaphorin 3E in prostate cancer.

AUTHOR: Williamson Magali(a); Masters John(a)

AUTHOR ADDRESS: (a)Institute of Urology, University College London, London
**UK

JOURNAL: Proceedings of the American Association for Cancer Research Annual
Meeting 42p522 March, 2001

MEDIUM: print

CONFERENCE/MEETING: 92nd Annual Meeting of the American Association for
Cancer Research New Orleans, LA, USA March 24-28, 2001

ISSN: 0197-016X

RECORD TYPE: Citation

LANGUAGE: English

SUMMARY LANGUAGE: English
2001

DESCRIPTORS:

ORGANISMS: 1542-CP3TX cell line (Hominidae...

?

? ds

Set	Items	Description
S1	62	PNT2 OR (ECACC(2N)95012613)
S2	6638182	TREAT? OR THERAP?
S3	16	S1 AND S2
S4	8	RD (unique items)
S5	0	NIH(W)1542
S6	6	CP3TX
S7	3	RD (unique items)

? s prostate(5n) (cell(w)line??)

Processing

150910 PROSTATE

4768304 CELL

2614078 LINE??

S8 7795 PROSTATE(5N) (CELL(W)LINE??)

? s s1 and s8

62 S1

7795 S8

S9 31 S1 AND S8

? s s9 and s6

31 S9

6 S6

S10 0 S9 AND S6

? s s1 and s6

62 S1

6 S6

S11 0 S1 AND S

? ds

Set	Items	Description
S1	62	PNT2 OR (ECACC(2N)95012613)
S2	6638182	TREAT? OR THERAP?
S3	16	S1 AND S2
S4	8	RD (unique items)
S5	0	NIH(W)1542
S6	6	CP3TX
S7	3	RD (unique items)

? s prostate(5n) (cell(w)line??)

Processing

150910	PROSTATE
4768304	CELL
2614078	LINE??

S8 7795 PROSTATE(5N) (CELL(W)LINE??)

? s s1 and s8

62	S1
7795	S8

S9 31 S1 AND S8

? s s9 and s6

31	S9
6	S6

S10 0 S9 AND S6

? s s1 and s6

62	S1
6	S6

S11 0 S1 AND S6

? s cancer or tumor

1211891	CANCER
1316026	TUMOR

S12 2148094 CANCER OR TUMOR

? s s9 and py<=1998

Processing

31	S9
33599898	PY<=1998

S13 3 S9 AND PY<=1998

? rd

>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.

...completed examining records

S14 3 RD (unique items)

? t s14/3,k,ab/1-3

14/3,K,AB/1 (Item 1 from file: 55)

DIALOG(R)File 55:Biosis Previews(R)

(c) 2003 BIOSIS. All rts. reserv.

11356383 BIOSIS NO.: 199800137715

Sodium channel protein expression enhances the invasiveness of rat and human prostate cancer cells.

AUTHOR: Smith Paul(a); Rhodes Nicholas R; Shortland Adam P; Fraser Scott P; Djamgoz Mustafa B A; Ke Youqiang; Foster Christopher S

AUTHOR ADDRESS: (a)Dep. Cellular Molecular Pathol., Univ. Liverpool, Liverpool L69 3GA**UK

JOURNAL: FEBS Letters 423 (1):p19-24 Feb. 13, 1998

ISSN: 0014-5793

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Expression of Na⁺ channel protein was analysed in established cell lines of rat and human prostatic carcinoma origin by flow cytometry

using a fluorescein-labelled polyclonal antibody. In many cell lines examined, the obtained frequency distribution profiles were bimodal and identified a subpopulation of cells which expressed high levels of Na!⁺ channel protein. A significant positive correlation was demonstrated between the proportion of channel-expressing cells and the functional ability of individual cell lines to invade a basement membrane matrix in vitro. In addition, two transfectant cell lines containing rat prostate cancer genomic DNA were found to express significantly elevated levels of Na!⁺ channel protein when compared with the original benign recipient cell line. Enhanced Na!⁺ channel expression by two metastatic derivatives of these transfectant cells directly correlated with increased invasiveness in vitro. These studies strongly support the hypothesis that expression of Na!⁺ channel protein and the metastatic behaviour of prostatic carcinoma cells are functionally related, either by endowing the membranes of these cells with specialized electrophysiological properties (e.g. enhancing their motility and/or secretory activities) and/or by perturbing endogenous mechanisms regulating ionic homeostasis within the cells.

1998

1998

...ABSTRACT: individual cell lines to invade a basement membrane matrix in vitro. In addition, two transfectant cell lines containing rat prostate cancer genomic DNA were found to express significantly elevated levels of Na!⁺ channel protein when...

DESCRIPTORS:

...ORGANISMS: PNT2 (Hominidae

14/3,K,AB/2 (Item 2 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

10871703 BIOSIS NO.: 199799492848
Anti-proliferative effects of phytoestrogens on human prostatic cell lines.
AUTHOR: Hempstock Joanne; Kavanagh John P; George Nicholas J R
AUTHOR ADDRESS: Manchester**UK
JOURNAL: Journal of Urology 157 (4 SUPPL.):p141 1997
CONFERENCE/MEETING: 92nd Annual Meeting of the American Urological Association New Orleans, Louisiana, USA April 12-17, 1997
ISSN: 0022-5347
RECORD TYPE: Citation
LANGUAGE: English
1997

1997

MISCELLANEOUS TERMS: ...HUMAN PROSTATE CANCER CELL
LINE; ...

...HUMAN SV40 IMMORTALIZED PROSTATE CELL LINE; ...

...PNT2 CELL LINE

14/3,K,AB/3 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2003 Inst for Sci Info. All rts. reserv.

03771550 Genuine Article#: QD772 Number of References: 42
Title: FUNCTIONAL EXPRESSION OF SV40 IN NORMAL HUMAN PROSTATIC EPITHELIAL
AND FIBROBLASTIC CELLS - DIFFERENTIATION PATTERN OF NONTUMORIGENIC
CELL-LINES (Abstract Available)

09/857, 690

RECEIVED 301

APR 01 2002

03923022 Genuine Article#: QR574 Number of References: 19
Title: TAG-72 EXPRESSION IN **PRIMARY, METASTATIC** AND HORMONALLY
TREATED **PROSTATE**-CANCER AS DEFINED BY MONOCLONAL-ANTIBODY CC49
(Abstract Available)

TECH CENTER 1600/2900

Author(s): BRENNER PC; RETTIG WJ; SANZMONCASI MP; REUTER V; APRIKIAN A; OLD
LJ; FAIR WR; GARINCHESA P

Corporate Source: MEM SLOAN KETTERING CANC CTR, DEPT SURG, UROL SERV/NEW
YORK//NY/10021; MEM SLOAN KETTERING CANC CTR, DEPT PATHOL/NEW
YORK//NY/10021; SLOAN KETTERING INST, PROGRAM IMMUNOL/NEW YORK//NY/00000
; LUDWIG INST CANC RES/NEW YORK//NY/00000

Journal: JOURNAL OF UROLOGY, 1995, V153, N5 (MAY), P1575-1579

ISSN: 0022-5347

Language: ENGLISH Document Type: ARTICLE

Abstract: Monoclonal antibodies CC49 and B72.3, which recognize a tumor
associated glycoprotein (TAG-72) related to sialylated Tn antigen, have
been used in clinical trials for radionuclide imaging, and treatment of
colon, breast and ovarian carcinoma. In addition, studies with CC49 in
patients with **metastatic** hormone refractory **prostate** cancer
have been initiated based on the observed expression of TAG-72 in
primary prostate cancer. We examined whether TAG-72
expression is a common feature of **primary, metastatic** and
hormonally treated prostatic carcinoma.

Immunohistochemical analysis of 25 **primary** prostatic
carcinomas confirmed previous data that 21 of 25 specimens (80%) were
immunoreactive with CC49. CC49 staining was noted in all 6 well
(Gleason score 2 to 4), 8 of 10 moderately (Gleason score 5 to 6) and 7
of 9 poorly (Gleason score 7 to 9) differentiated tumors. CC49
immunoreactivity was noted in 10 of 20 hormonally treated
prostate cancers and in 21 of 25 tumors without hormonal therapy.
Intense CC49 staining of prostatic intraepithelial neoplasia was
present in all 5 specimens examined. In contrast to the **primary**
lesion, many **metastatic prostate** cancers lacked detectable
CC49 immunoreactivity. Of 24 pelvic lymph node **metastases** from
different patients only 4 (17%) had significant CC49 staining and
5 others had rare CC49 positive cells. However, 6 of 12 bone
metastases showed CC49 immune staining. One specimen from an
anaplastic locally recurrent tumor showed no reactivity.

To our knowledge we present the first analysis of TAG-72 expression
in a large series of patients with hormonally treated and
metastatic prostate cancer, the most likely candidates for
CC49 immunotherapy. Our findings that lymph node and bone
metastases from **prostate** cancer are less likely to express
significant amounts of TAG-72 than **primary prostate** cancer
suggest that pretreatment biopsy typing for TAG-72 may be necessary to
optimize the results of ongoing CC49 imaging and therapy studies.

Title: TAG-72 EXPRESSION IN **PRIMARY, METASTATIC** AND HORMONALLY
TREATED **PROSTATE**-CANCER AS DEFINED BY MONOCLONAL-ANTIBODY CC49

...Abstract: treatment of colon, breast and ovarian carcinoma. In addition,
studies with CC49 in patients with **metastatic** hormone refractory
prostate cancer have been initiated based on the observed
expression of TAG-72 in **primary prostate** cancer. We
examined whether TAG-72 expression is a common feature of **primary**
, **metastatic** and hormonally treated prostatic carcinoma.

Immunohistochemical analysis of 25 **primary** prostatic
carcinomas confirmed previous data that 21 of 25 specimens (80%) were
immunoreactive with CC49...

...7 to 9) differentiated tumors. CC49 immunoreactivity was noted in 10 of
20 hormonally treated **prostate** cancers and in 21 of 25 tumors

without hormonal therapy. Intense CC49 staining of prostatic intraepithelial neoplasia was present in all 5 specimens examined. In contrast to the **primary** lesion, many **metastatic prostate** cancers lacked detectable CC49 immunoreactivity. Of 24 pelvic lymph node **metastases** from **different** patients only 4 (17%) had significant CC49 staining and 5 others had rare CC49 positive cells. However, 6 of 12 bone **metastases** showed CC49 immune staining. One specimen from an anaplastic locally recurrent tumor showed no reactivity...

...analysis of TAG-72 expression in a large series of patients with hormonally treated and **metastatic pr**

03012663 BIOSIS NO.: 000070038281

TUMOR ASSOCIATED ANTIGENIC DIFFERENCES BETWEEN THE PRIMARY AND THE

DESCENDANT METASTATIC TUMOR CELL POPULATIONS

AUTHOR: GORELIK E; FOGEL M; SEGAL S; FELDMAN M

AUTHOR ADDRESS: DEP. CELL BIOL., WEIZMANN INST. SCI., REHOVOT, ISR.

JOURNAL: J SUPRAMOL STRUCT 12 (3). 1979 (RECD. 1980). 385-402. 1979

FULL JOURNAL NAME: Journal of Supramolecular Structure

CODEN: JSPMA

RECORD TYPE: Abstract

LANGUAGE: ENGLISH

ABSTRACT: The existence of antigenic differences between cell populations in the local growth of the 3LL [lung carcinoma] tumor (L-3LL) and its lung metastases (M-3LL) was studied. Normal C57BL/6 spleen cells sensitized in vitro for 5 days against L-3LL monolayers lysed preferentially L-3LL targets but not M-3LL tumor cell targets. Conversely, anti-M-3LL-sensitized lymphocytes killed M-3LL targets more efficiently than they killed L-3LL targets. Spleen cells from mice bearing subcutaneous L-3LL tumors were significantly more cytotoxic to L-3LL targets than to M-3LL targets and vice versa. M-3LL cells were more resistant in vitro and in vivo to natural killer cells than were L-3LL tumor cells. M-3LL cells were more resistant than L-3LL cells to hybrid resistant mechanisms when they were inoculated into F1 (C3Heb .times. C57BL/6) or F1 (BALB/c .times. C57BL/6) mice. Anti-M-3LL lymphocytes generated both in vitro and in vivo, but not anti-L-3LL lymphocytes, admixed with L-3LL or M-3LL tumor cells and inoculated into footpads of syngeneic recipients suppressed the development of lung metastases. Metastatic cells are phenotypic variants of the local growing tumor cell populations. Presumably, these variants are selected for their capacity to home to and grow in the lungs, and for their resistance to specific immune effects initially evoked against the local tumor and to nonspecific natural killer cells. These data may be of importance with respect to any rational approach to the problem of immunotherapy.

said, "but it is likely to be only one means to an end, not the end itself."

COPYRIGHT 1999 American Medical Association

DESCRIPTORS: Vaccines industry--Product development; Antineoplastic agents

--Product development

GEOGRAPHIC CODES/NAMES: 1USA United States

PRODUCT/INDUSTRY NAMES: 2834140 (Anticancer Drugs); 2831200 (Vaccines & Antigens for Human Use)

NAICS CODES: 325412 Pharmaceutical Preparation Manufacturing; 325414

Biological Product (except Diagnostic) Manufacturing

FILE SEGMENT: TI File 148

6/19/2 (Item 2 from file: 149)

DIALOG(R)File 149:TGG Health&Wellness DB(SM)

(c) 2002 The Gale Group. All rts. reserv.

01735055 SUPPLIER NUMBER: 20049410 (THIS IS THE FULL TEXT)

Allogeneic vaccines may be viable alternative to autologous vaccines.

Marble, Michelle

Cancer Weekly Plus, p4(2)

Nov 24,

1997

PUBLICATION FORMAT: Newsletter LANGUAGE: English RECORD TYPE: Fulltext

TARGET AUDIENCE: Professional

WORD COUNT: 374 LINE COUNT: 00034

TEXT:

Success in animal models suggests that allogeneic cell cancer vaccines may be an effective alternative to autologous cell cancer vaccines.

The use of autologous cell cancer vaccines in clinical practice is limited by the invasive nature of harvesting cells, as well as the difficulty and expense of culturing and processing these cells. Justina Kayaga, representing colleagues from the St. George's Hospital Medical School, the Kings College School of Medicine and Dentistry, and the Royal Marsden Hospital, United Kingdom, presented results from animal studies using an alternative allogenic melanoma cell vaccine at the 3rd European Conference on Gene Therapy of Cancer, held September 11-13, 1997, in Berlin, Germany.

"To date, autologous whole cell tumor vaccines have yielded very limited results and are associated with a number of inherent difficulties which make them impractical for wide scale clinical use," stated Kayaga et al. in an abstract submitted to the conference ("Allogeneic Vaccination -

A Viable Alternative to Autologous Vaccination?"). "Thus, strong attention has now been focused on allogeneic vaccines which offer the advantage of being more practical and reproducible."

The researchers used the B16-F10 (h-2b) murine model of melanoma. Vaccination with wild type allogeneic K1735-M2 cells (H-2k) conferred a specific protective immune response in 40-60 percent of the animals vaccinated. T-cell proliferation experiments supported their observations.

They also used the rat (Lobund Wistar) model of prostate cancer . Vaccination with the wild type allogeneic Copenhagen rat MATLyLu cells prevented the establishment of PAIII tumors in 80 percent of the animals vaccinated.

~"Taken-together, these results suggest that allogeneic vaccination may have a role in other cancers as well as in melanoma," concluded Kayaga et al. "Finally, we have transfected both B16-F10 and K1735-M2 cell lines with GMCSF (granulocyte macrophage colony stimulating factor) and we are now carrying out studies to show whether or not allogeneic vaccines can be as effective in the treatment of established tumors as their autologous counterparts."

The corresponding author for this study is Justina Kayaga, Division of Oncology, Department of Cellular and Molecular Sciences, St. George's Hospital Medical School, Cranmer Terrace, London, United Kingdom.

COPYRIGHT 1997 Charles W Henderson

01866696 SUPPLIER NUMBER: 56979429 (THIS IS THE FULL TEXT)

Uncovering cancer's.

MORAN, MARK

American Medical News, 42, 39, 23

Oct 18,

1999

PUBLICATION FORMAT: Magazine/Journal ISSN: 0001-1843 LANGUAGE: English

RECORD TYPE: Fulltext TARGET AUDIENCE: Professional

WORD COUNT: 1913 LINE COUNT: 00154

TEXT:

Despite past disappointments and some skepticism, scientists hope they can induce an immunologic response to cancer with a therapeutic vaccine.

THIRTY-ONE YEARS AGO, STEVEN ROSENBERG, MD, THEN A resident at Peter

Bent Brigham Hospital in Boston, encountered what appeared to be a medical miracle: a cancer patient whose malignancy vanished, apparently destroyed by the patient's own immune system.

The event was the genesis of a lifelong scientific quest: to induce an immunologic response to cancer, ultimately through the use of a therapeutic vaccine. Dr. Rosenberg has not been alone in that quest, nor was he the first to envision the cancer-fighting potential inherent in the body's own defenses. It is an effort that dates to the turn of the century.

Yet the vision of a cancer vaccine has repeatedly been thwarted by an insidious characteristic of tumors: chameleonlike, they appear to the body's immune system little different from healthy cells.

"The obstacles are the same as they have always been, namely that tumors are not so different from normal cells," said David Berd, MD, of the division of medical oncology at the department of medicine at Thomas Jefferson University School of Medicine. "That's a shocking idea considering the terrible nature of the disease, but on a chemical level it's hard to find major differences between tumors and normal cells. All of immunology is based on differences from one cell to another."

Today, groundbreaking advances in immunology are reaping a harvest of hope for vaccines. Researchers at cancer centers around the country are on the trail of tumor antigens, the molecules on cells recognized by the immune system as foreign that induce an immune response. Several multisite trials have been initiated for a variety of vaccine strategies.

Still, some clinicians are skeptical of the enterprise, saying real hope for cancer patients lies elsewhere.

Stanley E. Order, MD, clinical professor of radiation oncology at Stony Brook University Medical Center, State University of New York, called the current buzz about vaccines "Wall Street enthusiasm" and said the antigens touted as keys to inducing an immune response are found in normal

cells as well. "I am skeptical for the simple reason that (researchers) don't have specific products that are unique to human tumors," Dr. Order said.

Prophecies of a vaccine may distract professionals and the public from more realistic innovations that are on the horizon, Dr. Order said. These include gene therapy and antiangiogenesis, the use of agents to inhibit the creation of new blood vessels by a tumor.

Nevertheless, the lure of a cancer vaccine is compelling, both for its scientific elegance and its obvious potential advantages over surgery, chemotherapy and radiation. Researchers, though chastened by disappointments of the past, are hopeful.

"People have been doing this for a long time, and enthusiasm runs in cycles," Dr. Berd said. "Right now there is a peak of enthusiasm, but this time we are going into it with our eyes open and without delusions. I hope we are going to make a hit and find a treatment that will become a part of the standard cancer regimen."

Multiple approaches

VACCINE EFFORTS MAY BE ROUGHLY divided into those that seek to immunize patients using a whole tumor cell, containing any number of antigens, and those that seek to immunize with specific antigens. For a variety of reasons, researchers have focused on melanoma because it has a high rate of spontaneous remission, suggesting that it may be particularly susceptible to an immune response, and melanoma cells are accessible and easy to grow in the lab. But vaccine efforts are also targeting breast, ovarian and prostate cancers.

Scientists at the National Cancer Institute have reported a successful human trial of a vaccine for B-cell lymphoma (Nature Medicine, October). Of 20 patients in remission after chemotherapy, 19 showed tumor-specific cytotoxic T cells after receiving the vaccine plus an immune-system booster. And in 11 patients with evidence of microscopic disease following chemotherapy, eight were free of residual tumor after vaccination.

Dr. Berd's work is an example of the whole - cell approach, using an autologous vaccine. The strategy is based on animal research in which he found that melanoma tumors in animals regressed when the animals were injected with their own cancer cells, modified with a hapten, a chemical that stimulates an immune response when attached to a protein. It is a quintessential example of immunotherapy for cancer: by modifying tumors with a radically foreign substance, the immune system is "tricked" into responding to that which it would not normally recognize as foreign.

Dr. Berd's vaccine presents native tumor cells with all the antigens specific to that patient's cancer. And therein lay the advantage of using autologous cells: whatever antigens are required to induce an immune response are likely to be contained within the patient's own tumor.

Human trials using the autologous whole - cell approach are promising. In about 200 patients with metastatic melanoma to the lymph

nodes that has been surgically removed -- but who likely have microscopic deposits of melanoma somewhere in the body -- the vaccine has significantly enhanced survival. And in a small number of patients with surgically inoperable melanoma, Dr. Berd found regression of small lung metastases and greatly enhanced survival.

A multisite randomized trial, sponsored by AVAX Technologies, a biotechnology company in Kansas City, Mo., will compare the autologous whole - cell vaccine vs. standard treatment with interferon.

Another example of the whole - cell approach, using cells grown in culture, is the strategy pursued by Donald Morton, MD, medical director and surgeon-in-chief at John Wayne Cancer Institute, Santa Monica, Calif. Dr. Morton's work dates to the mid-1960s, when he and colleagues found that melanoma nodules in the skin -- as well as those at distal sites -- would regress when the nodules were injected with bacillus Calmette-Guerin, a tuberculosis germ from cattle.

Those early successes led to the idea of growing tumor cells in tissue culture, irradiating them and giving them to patients in a vaccine mixed with BCG. By the early 1980s, Dr. Morton had targeted six antigens to which patients formed antibodies when vaccinated. By selecting cell lines with a high content of those six antigens, he was able to develop an antigen-enriched vaccine. That polyvalent vaccine using whole cells has since been shown to contain 20 antigens capable of inducing an immune response in melanoma, Dr. Morton said.

Nonrandomized controlled trials in humans have shown that approximately 90% of patients receiving the vaccine develop a significant immune response, and that those who respond survive three times longer than those who do not respond. "The data suggest the antigen responsible for the clinical response will differ from patient to patient, depending upon which antigen is present in their particular melanoma," Dr. Morton said. "That's why activation of immune response to multiple antigens by a polyvalent vaccine is important."

Currently, a five-year multicenter randomized trial is testing the effectiveness of the vaccine. In the study, one group of patients will get BCG plus placebo and a second will receive BCG plus the antigen-enriched vaccine. In contrast to the whole - cell approach are strategies focusing on specific antigens. At Memorial Sloan-Kettering Cancer Center, Philip O. Livingston, MD, and colleagues began searching for a melanoma antigen 20 years ago by immunizing patients with cancer cells that had been disabled by radiotherapy. Only a few patients had immune responses, and the only antigen recognized by more than one person's immune system was an antigen known as GM2.

In a fashion similar to efforts by Drs. Berd and Morton, the GM2 molecule is attached to a substance that is radically foreign to the immune system -- in this case a clam blood molecule -- thereby promoting an immune response to the melanoma. Dr. Livingston enhances the vaccine with an immune-boosting substance from the bark of a South American tree.

Since then, Dr. Livingston has found other specific antigens that prompt an immune response in patients with melanoma, breast, prostate and ovarian cancer. Randomized controlled trials with polyvalent vaccines having three to five different antigens are scheduled to begin later this year.

In what may be the most sophisticated effort, immunotherapy for cancer promises to marry breakthroughs in immunology with those in genetics, offering hope for a form of "individualized medicine" aimed at cancer patients. At this level of innovation, Dr. Rosenberg and colleagues at the National Cancer Institute are targeting the genetic material of proteins on cancer cells recognized by the body's immune system.

The effort builds on work in the 1980s using Interleukin-2 to induce tumor-infiltrating lymphocytes believed to attack tumors. Those cells were then harvested, grown in large numbers and returned to patients as a direct attack against tumors.

Now, Dr. Rosenberg has identified the genes that code for antigens recognized by tumor-infiltrating lymphocytes and is cloning them for use in vaccines specially prepared for the individual cancer patient. In a study in *Nature Medicine* (March 1998), 13 of 31 patients with metastatic melanoma who received the vaccines experienced tumor regression. Multisite trials scheduled to begin later this year will compare use of the vaccine plus IL 2, with IL2 alone.

"We are identifying the exact molecules the immune system recognizes and immunizing patients against them," Dr. Rosenberg said. "That's where I see this new era of immunotherapy going. For the first time, we don't have to depend on the entire cell, which contains tens of thousands of different proteins. We can immunize against the specific ones we need."

Between the most extravagant hopes of scientists and the skepticism engendered by past failures, there may be a middle ground for the cancer vaccine: as one weapon in an arsenal that will need to be as heterogeneous as the disease itself.

Michael Gordon, MD, associate professor of medicine at Indiana University School of Medicine and a clinician at the Indiana University Cancer Center, said vaccine would probably be used as an adjunct to surgery in patients with a high likelihood of relapse. But he echoed the crucial limitation of vaccines so far: immunologic response does not mean a cure.

"From the clinical point of view, immune response is the starting point, not a finish," he said. "Patients who have immune responses tend to do somewhat better than those who don't respond at all. That makes sense, but it's defined by their living longer, not necessarily by their cancer shrinking."

He suggested that any vaccine is likely to require addition of immunotherapeutic agents to enhance efficacy. And ultimately vaccines may be used in combination with other emerging therapeutic possibilities, including gene therapy and anti-angiogenic therapy. "Vaccines represent a new and exciting treatment option for patients with cancer," Dr. Gordon